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		Official page numbers:
CONSENSUS STATEMENT REGARDING THE HIV "WINDOW PERIOD"	F-1	213 – 215
SURROGATE MARKERS OF HIV INFECTION	F-2	215 – 216
INTERIM GUIDELINES FOR THE TREATMENT OF GONOCOCCAL AND CHLAMYDIAL INFECTIONS	F-3	216 – 220

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CONSENSUS STATEMENT REGARDING THE HIV "WINDOW PERIOD"

Preamble

On 16 November, 1994, the combined National HIV Epidemiology and Laboratory Consensus Meeting (40 to 50 participants) considered the scientific evidence for defining the period of time following exposure and infection with HIV and the generation of detectable antibodies by the infected person, i.e., the so-called "window period". The following is the consensus statement that was reached following consideration of the available information and lengthy discussion.

Studies of the natural history of HIV infection have defined a period of time following exposure and infection when the infected person has not yet generated a detectable antibody response. During this time, current antibody tests cannot detect the presence of the infection in spite of recent improvements in sensitivity.

Studies to evaluate the length of the window period have several limitations.

- Often little information is available on the precise time of the exposure (except in some situations such as occupational exposure to HIV-infected blood-body fluids due to a needle stick), the occurrence of infection, or the period of infectiousness.
- A limited number of scientific studies over time have used 1st, 2nd, and 3rd generation HIV antibody tests to determine the duration of the window period. The increased sensitivity of 3rd generation tests has reduced the time duration of the window period[1].
- The total number of patients studied worldwide in retrospective blood transfusion-related studies, prospective seroconversion studies, or as individual case reports probably does not exceed 300.
- There is considerable uncertainty about the nature of the distribution of window periods given the large amount of variability in the immune response among infected persons.
- There are no reliable data on whether or not there is a significant "tail" representing persons with very long window periods, extending well beyond the estimated mean time to seroconvert. To date, reports of excessively long incubation periods, have been refuted and withdrawn by the original authors[2,3]. However, the possibility still exists that a few individuals may seroconvert well beyond the estimated mean time. The small number of persons studied created some uncertainty regarding the mean of the distribution as well.
- There are anecdotal and case reports in the scientific literature reporting window periods that extend beyond 3 months following exposures. However, there is usually a lack of information regarding the viral inoculum, the type of virus, the type and timing of the exposure, the route of transmission, etc., to enable accurate interpretation of these reports.

Newly developing technologies to detect the presence of HIV directly without reliance on the development of antibodies are not yet accessible for general use to shorten the window period from weeks to perhaps days. Until newer technologies are available, antibody testing will continue to be the principal approach for diagnosing HIV infection.

The Canadian Medical Association's statement on the HIV Window Period has defined it as follows:

"The enzyme-linked immunosorbent assay (ELISA) rarely fails to detect serum HIV antibodies when they are present. A negative ELISA indicates that HIV antibodies were not detected. This means that either the patient is not infected or the patient is in the "window period" between HIV infection and the beginning of antibody production. This window period may last up to 6 months, although 95% of adults will seroconvert (develop HIV antibodies) within 3 months."[4]

After reviewing the available data and discussing the uncertainties that exist in the scientific literature, the participants agreed on the following statements:

1. Although there are uncertainties regarding the nature of the distribution of the window period due to the limited scientific information available, it is clear that the majority of HIV-infected persons will develop detectable antibodies within 2 to 8 weeks after infection. It is most likely that 97% or more will develop antibodies in the first 3 months following the time of their infection.
2. To define the window period further, a national strategy is required to examine existing HIV databases retrospectively, to study persons known to have seroconverted, and to develop collaborative prospective studies.
3. Since the possibility exists that HIV seroconversion may occur beyond 3 months following the time of exposure or infection, the following procedures are advisable:
   - All tissues and organs (including sperm) from HIV- negative organ donors that can be stored for extended periods prior to use should be stored for at least 6 months, and the donor should be retested immediately prior to transplanting the tissues. Except in life-threatening situations, potential HIV-negative organ donors should be retested 6 months after their donation prior to transplanting the organ.
   - Persons who seek HIV testing because of a recent suspected exposure (as opposed to life-long or extended exposure, such as an injection drug user or a person with persistent high-risk behaviour), should be retested 3 months after their initial negative test. At the 3-month point, they may be counselled that it is unlikely (but not impossible) that they are HIV-infected. All persons who test negative at the 3-month point should be retested at the 6-month point to be certain that they are truly negative.
4. All blood, tissue and organ donors should continue to defer donation if they have any reason to suspect that they are at increased risk for HIV infection.

References

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4. Canadian Medical Association. *Counselling guidelines for human immunodeficiency virus serologic testing*. Ottawa: Canadian Medical Association, 1993:2.

SURROGATE MARKERS OF HIV INFECTION

The following statement is based on the consensus statement by the Scientific Advisory Committee on Surrogate Markers of HIV, prepared during a U.S. Food and Drug Administration Symposium on Surrogate Markers of HIV, 13-14 October, 1994, in Washington, D.C. The Advisory Committee consisted of a panel of clinical investigators and representatives of the community, industry and the Food and Drug Administration.

Since HIV infection begins the HIV disease process, the relevance and application of markers of disease progression is critical to clinical management. In addition, clinical trials of new therapies often depend on surrogate endpoints based on markers of disease progression.

In cross-sectional studies, all of the following surrogate markers correlate with disease progression:

- **Immunologic markers** — CD4 count; CD4 percentage; beta-2 microglobulin; and neopterin.
- **Virologic markers** — p24 antigen; immune complex dissociated p24; viral culture titre; DNA PCR; RNA PCR; genotypic or phenotypic measures of drug resistance; and biologic phenotype (non-syncytium inducing/syncytium inducing).
- **Lymphocyte function** — proliferative responses (specific and nonspecific); and cytokine elaboration.

A change in any of the above markers indicates an effect of a drug in vivo. The absence of effect on proviral load (as measured by DNA PCR) or genotypic or phenotypic markers of drug resistance or biologic phenotype, however, may not indicate a lack of antiviral drug effect.

The Committee suggested that the most promising surrogate marker for further research and earliest clinical application is plasma viremia (as measured by RNA PCR or branched DNA). Other promising measures include continued use of CD4 cell counts and percentages, newer functional immunologic assays, circulating viral titre (infectious units/10^6 mononuclear cells), proviral load (quantitative DNA PCR), cell-associated messenger RNA quantification, genotypic and phenotypic measures of drug resistance and lymph node viral loads.

Although viral quantitation is a useful prognostic marker of HIV disease progression in research settings, it is not yet known whether measurements of viral load can be used to guide individual therapeutic management. Validation for this application will require correlation with hundreds (perhaps thousands) of clinical events. This information is needed to establish the independent prognostic significance of any given laboratory marker, including viral quantitation in blood or other tissues.

The same Committee met again in McLean, Virginia, 16-18 October, 1995. After reviewing available data generated in the past year, it was concluded that, although significant progress has been made, further work is still needed to fully validate plasma viremia as a surrogate marker for use in individual patient management.

INTERIM GUIDELINES FOR THE TREATMENT OF GONOCOCCAL AND CHLAMYDIAL INFECTIONS

The 1995 Update of the Canadian Guidelines for the Prevention, Diagnosis, Management and Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults should be available early in 1996. In the interim, the Division of STD Control, Bureau of HIV/AIDS and STD, Laboratory Centre for Disease Control, in consultation with the Expert Working Group* on the 1995 Update, has decided to publish the treatment guidelines for gonococcal and chlamydial infections.

The treatment guidelines for gonococcal infection have been revised to reflect the increased prevalence of antimicrobial resistance. All gonococcal infections are treated presumptively as if they were resistant. Penicillin, ampicillin, amoxicillin, and tetracyclines are no longer recommended as therapy for gonorrhea. The antibiotics currently recommended for first-line therapy, the third generation cephalosporins (ceftriaxone and cefixime) and the fluoroquinolones (ciprofloxacin and ofloxacin), are efficacious against *N. gonorrhoeae* strains resistant to penicillin and tetracycline. The dosage levels for ceftriaxone and cefixime have been reduced by 50% from those indicated in the 1992 STD treatment guidelines.

All patients treated for gonococcal infection should also be treated with an antimicrobial effective against chlamydia, such as doxycycline or azithromycin, unless tests for chlamydia are known to be negative. Azithromycin, a single dose therapy, has been added as a first-line treatment for chlamydial infections in adults and adolescents.

The changes have been endorsed by the Canadian Infectious Disease Society's Sub-Committee on Sexually Transmitted Diseases and the Canadian Paediatric Society's Committee on Infectious Diseases and Immunization.

Table 1
Treatment of gonococcal infections in adolescents and adults (except pregnant women and nursing mothers)[a]

***NOTE**: All patients treated for gonorrhea should also be treated for chlamydial infection.*

Urethral, endocervical, rectal, pharyngeal infection

*All regimens followed by doxycycline/tetracycline/azithromycin**

Preferred (IM):
- **ceftriaxone 125 mg IM** in a single dose

Preferred (oral) (alphabetic order):
- **cefixime 400 mg orally** in a single dose

OR
- **ciprofloxacin 500 mg orally** in a single dose

OR
- **ofloxacin 400 mg orally** in a single dose

Alternative (IM): except pharyngeal
- **spectinomycin 2 g IM** in a single dose

PLUS
- **doxycycline/tetracycline/azithromycin**

Gonococcal ophthalmia (adolescent and adult)
Disseminated infection: arthritis, meningitis

Consultation with a specialist is essential. Hospitalization is necessary for meningitis and may be necessary for other disseminated infection.

Preferred initial therapy:
- **ceftriaxone 2 g/day IM or IV**

PLUS doxycycline/tetracycline/azithromycin while awaiting consultation

N.B.: All patients should also receive empiric treatment for chlamydial and non-gonococcal infections with doxycycline 100 mg orally x 2/day for 7 days or tetracycline 500 mg orally x 4/day for 7 days.

* Azithromycin 1 g orally in a single dose is an alternative for the empiric treatment of chlamydia. There are only limited data, as yet, to support the use of azithromycin in non-gonococcal/non-chlamydial urethritis or cervicitis; more studies are currently being carried out.

(a) Ceftriaxone and cefixime should not be given to persons with cephalosporin allergy or a history of immediate and/or anaphylactic reactions to penicillins.

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Table 2
Treatment of gonococcal infections in pregnant women and nursing mothers

Urethral, endocervical, rectal or pharyngeal infection

The treatment regimens for adolescents and adults should be followed except that ofloxacin and ciprofloxacin are contraindicated and doxycycline/tetracycline, azithromycin should be replaced by **erythromycin 2 g/day** in divided doses for at least 7 days OR, if not tolerated, **erythromycin 1 g/day** in divided doses for 14 days may be substituted (erythromycin estolate is contraindicated in pregnancy). Amoxicillin 3 g orally or ampicillin 3.5 g orally with probenecid 1 g orally can be considered if isolate is known to be sensitive.

Table 3
Treatment of gonococcal infections in children < 9 years[a,b]

Urethral, vaginal, rectal, pharyngeal infection

Preferred:
- **cefixime 16 mg/kg orally** in a single dose (max 400 mg)(b)

PLUS erythromycin

OR

ceftriaxone 125 mg IM in a single dose

PLUS erythromycin

Alternative: except pharyngeal
- **spectinomycin 40 mg/kg IM** (max 2 g) in a single dose

PLUS erythromycin

Disseminated infection: arthritis, meningitis, gonococcal ophthalmia beyond neonatal period

Hospitalization and consultation with a specialist is essential.

Preferred initial therapy:
- **ceftriaxone 50-100 mg/kg/day IM or IV**

PLUS erythromycin while awaiting consultation

N.B. Erythromycin 40 mg/kg/day orally in divided doses (max 500 mg x 4/day) for 7 days as treatment for chlamydial infection should always be included.

NOTES

(a) Ceftriaxone and cefixime should not be given to persons with cephalosporin allergy or a history of immediate and/or anaphylactic reactions to penicillins.

(b) Oral therapies are preferred in children. Recommendations for the use of cefixime are based on data showing efficacy in the treatment of infections caused by organisms similar to *Neisseria gonorrhoeae*. Because there is limited experience with the use of cefixime in children with gonococcal infections, antimicrobial susceptibility *must* be ascertained AND follow-up culture assured. If follow-up cannot be assured, use ceftriaxone 125 mg IM in place of cefixime.

Table 4
Treatment of gonococcal infection in neonates

Ophthalmia Neonatorum

Hospitalize and institute appropriate infection control precautions until 24 hrs of effective therapy completed.
- culture eye discharge, blood (CSF *only if evidence of systemic disease*)
- irrigate eyes immediately with sterile normal saline and at least hourly as long as necessary to eliminate discharge
- start ceftriaxone 50-100 mg/kg/day IV or IM (single dose therapy may be adequate if blood culture is negative)
- consult with a specialist as soon as possible

Newborns born to women infected with gonorrhea

Recommended therapy (must also include therapy for chlamydia for 14 days):

- **ceftriaxone 125 mg IM** in a single dose PLUS erythromycin in the following dosage schedule
  –if < 7 days of age and < 2000 g
  erythromycin 20 mg/kg/day orally in divided doses
  –if < 7 days of age and > 2000 g
  erythromycin 30 mg/kg/day orally in divided doses
  –if > 7 days of age
  erythromycin 40 mg/kg/day orally in divided doses

Other points
- The preferred diluent for IM ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.
- In adults, if tetracyclines are contraindicated or not tolerated, use **erythromycin 2 g/day orally** in divided doses for 7 days (1 **g/day** in divided doses for 14 days if higher dose not tolerated). Other formulations of erythromycin can be substituted in appropriate doses except that erythromycin estolate is contraindicated during pregnancy.
- Erythromycin dosages refer to erythromycin base. Equivalent dosages of other formulations may be substituted.

Table 5
Treatment of chlamydial infections (Urethral, endocervical, rectal infection)

ADOLESCENTS AND ADULTS [except pregnant women and nursing mothers]	
Preferred: – **doxycycline 100 mg orally** x 2/day for 7 days OR – **azithromycin 1 g orally** in a single dose	*Alternative:* If tetracycline is tolerated **tetracycline 500 mg orally** x 4/day for 7 days OR for patients for whom tetracyclines are contraindicated or not tolerated – **erythromycin 2 g/day orally** in divided doses for 7 days OR **If that regimen is not tolerated** – **erythromycin 1 g/day orally** in divided doses for 14 days OR try another formulation of erythromycin OR – **sulfamethoxazole 1 g orally** x 2/day for 10 days OR – **ofloxacin 300 mg bid** for 7 days
PREGNANT WOMEN AND NURSING MOTHERS	
Preferred: – **erythromycin 2 g/day orally** in divided doses (erythromycin estolate is contraindicated) for 7 days OR If that regimen is not tolerated – **erythromycin 1 g/day orally** in divided doses for 14 days OR try another formulation of erythromycin	*Alternative in first 2 trimesters:* – **sulfamethoxazole 1 g orally** x 2/day x 10 days *Alternative in last trimester:* – **amoxicillin 500 mg orally** x 3/day for 7 days (limited data exist concerning the efficacy of this regimen)

Table 6
Treatment of chlamydial infections, in newborns, infants and children

NEWBORNS AND INFANTS*	CHILDREN	
	< 9 years	≥ 9 years
During first week of life: infants < 2000 g – **erythromycin 20 mg/kg/day orally** in divided doses infants > 2000 g – **erythromycin 30 mg/kg/day orally** in divided doses *> 1 week to 1 month* – **erythromycin 40 mg/kg/day orally** in divided doses ***The above regimens should be given for at least 14 days.*** **N.B.**: Topical therapy alone for conjunctivitis is NOT adequate.	*After 1 month of age* – **erythromycin** **40 mg/kg/day orally** in divided doses (max 500 mg x 4/day) for 7 days OR – **sulfamethoxazole** **75 mg/kg/day orally** in divided doses (max 1 g x 2/day) for 10 days	*Preferred:* – **doxycycline** **5 mg/kg/day orally** in divided doses (max 100 mg x 2/day) for 7 days OR – **tetracycline** **40 mg/kg/day orally** in divided doses (max 500 mg x 4/day) for 7 days *Alternative:* for patients for whom tetracyclines are contraindicated or not tolerated – **erythromycin** **40 mg/kg/day orally** in divided doses (max 500 mg x 4/day for 7 days or 250 mg x 4/day for 14 days) OR – **sulfamethoxazole** **75 mg/kg/day orally** in divided doses (max 1 g x 2/day) for 10 days

NOTES

* Newborns and infants born to infected women must be tested and treated.
– Erythromycin dosages refer to the use of erythromycin base. Equivalent dosages of other formulations (except the estolate which is contraindicated in pregnancy) may be substituted.
– If erythromycin has been used for treatment, repeat testing after completion of therapy is advisable.

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